

**REMARKS/ARGUMENTS**

Applicant responds to the Examiner's comments using the paragraph numbering of the office action. Support for the recital that the immune response to an amyloid component includes antibodies in amended claim 11 is provided at *e.g.*, p. 13, lines 10-25. Support for an adjuvant that augments an immune response is provided at *e.g.*, p. 11, lines 10-15. Support for new claim 58 is provided, *e.g.*, Table 2, p. 4. Unless otherwise indicated amendments are for purposes of clarity. No amendment should be construed as an acquiescence in any ground of rejection.

1. Traverse of the restriction requirement is maintained for the reasons previously indicated. However, the requirement is moot in view of the amendments to the claims.

4-6. Information disclosure statement.

Applicant's citation of the citation nos. 144, 162, 174, and 186 include all the elements required to comply with 37 C.F.R. §§ 1.97-98 that are known. The Examiner commented that citation no. 187 was not present in the information disclosure statement. A supplemental information disclosure statement and PTO/SB/08A form citing and enclosing citation no. 187 is submitted herewith.

7. Specification.

The specification was objected to as having informalities. Applicant has amended the specification to correct informalities and requests that the objection be withdrawn.

The cross reference to related application section has been replaced with a replacement section which provides domestic priority information for the instant case. A supplemental ADS providing domestic priority information is submitted herewith to satisfy the specific reference requirement of 35 U.S.C. § 119(e) and § 120.

The addition of page 96, which was inadvertently omitted from the instant application as filed, to the specification does not add new matter. The instant application

incorporates U.S. Application No. 60/137,010 by reference (*see* p. 2, lines 5-6 of the instant application). Support for the addition of page 96 is provided at page 87, line 29 to page 88, line 20 of U.S. Application No. 60/137,010. For the convenience of the Examiner, applicant has attached pages 87 and 89 of U.S. Application No. 60/137,010 as Exhibit A. Page 96 is attached as Exhibit B.

As requested by the Examiner, the brief description of the drawings section of the specification has been amended to recite a brief description of Figs. 15A, 15B, 15C, 15D, and 15E.

The specification has also been amended to conform to five of the replacement drawing sheets submitted herewith, *i.e.*, Fig. 15A, Fig. 15B, Fig. 15C, Fig. 15D, and Fig. 15E, respectively. The paragraph beginning on page 10, line 26, has been replaced with six replacement paragraphs. The replacement paragraphs describe Figures 15A-15E, 15A, 15B, 15C, 15D, and 15E, respectively. The paragraph beginning on page 94, line 1, has also been amended to identify Figures 15A-15E.

The paragraphs beginning on page 91, line 17, and page 92, line 3, have been amended to conform the alum concentration to the alum concentration recited in Figure 15 as filed in Application No. 09/201,430, filed November 30, 1998. The instant application claims priority to Application No. 09/201,430.

#### 8. Sequence rules.

The office action mailed November 27, 2002 enclosed a notice to comply with the sequence listing rules. On May 23, 2003, applicant brought the instant application into compliance with the sequence rules by submitting the following papers to the Office, via Express Mail Post Office to Addressee, in an envelope addressed to Mail Stop Sequence, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450: a paper copy of the Sequence Listing, an electronic copy of the Sequence Listing, and an Amendment under 37 C.F.R. §§ 1.821-1.825.

9. Drawings.

Amendments to Figure 11

As requested by the Examiner, Figure 11 has been amended to add a legend. Support for this amendment can be found at page 77, line 17 to page 78, line 29 of the specification.

Amendments to Figures 15A-15E

As requested by the Examiner, the brief description of the drawings section of the specification has been amended to recite a brief description of Figs. 15A, 15B, 15C, 15D, and 15E.

Figures 15A-15E have been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Figure 15D as filed in the instant application discloses an alum concentration of 2 $\mu$ g/ml. Amended Figure 15D discloses an alum concentration of 2 mg/ml. Support for both of these amendments is provided by the informal Figure 15 as originally filed in the parent application. Thus, the amendments to the Figs. 15A-E contain no new matter.

Amendments to Figure 16

The descriptive term "Anti AB" has been replaced with the term "Anti-Abeta" to give greater clarity to the title. Support for this amendment can be found on page 92, lines 25-33 of the specification.

10-20. Rejections under 35 U.S.C. § 112, first paragraph. Due to the length of this rejection applicant will address each paragraph in turn starting with paragraph 11.

11. The Examiner alleges that the specification is enabling for treating Alzheimer's disease by administration of A $\beta$ 1-42 with an adjuvant in mouse models but does not reasonably enable treating any disorder characterized by amyloid deposition with any fibril protein or peptide. Applicant disagrees but as this paragraph merely represents a summary of the

Examiner's subsequent paragraphs will provide their reasoning in addressing these subsequent paragraphs.

12. The Examiner merely summarizes the claims. No response is required.

13. The Examiner alleges that the PDAPP mouse model does not exhibit Alzheimer's disease, Down's syndrome or other amyloidogenic disease as evidenced by Schenk, Games, and Chen. Insofar as the Examiner is suggesting that the PDAPP mouse model is not a good model of Alzheimer's disease or Down's syndrome in humans, Applicant disagrees. The PDAPP mouse used in the present examples has been recognized in the art as being a major breakthrough in the production of an animal model for Alzheimer's disease. The importance and breakthrough nature of the PDAPP mouse is indicated by the fact it was the cover story in that edition of *Nature* in which it was first described (Games *et al.*, *Nature*, 373(6514):523-527 (1995)). PDAPP transgenic mice described in Games exhibit age- and brain region-dependent development of typical amyloid plaques, dystrophic neurites, loss of presynaptic terminals, astrogliosis and microgliosis. These lesions in the PDAPP mouse brain tissue typify many of the neuropathological hallmarks associated with Alzheimer's disease. Games also describes neurodegeneration and inflammation characteristic of Alzheimer's disease, with associated A $\beta$  plaque deposition and certain regions of afflicted brain parenchyma which are present in the mice genetically engineered with the construct. Deposition of brain deposits increases with age, as in the case of Alzheimer's disease. Thus, the PDAPP mouse does model much of the pathology seen in Alzheimer's disease patients.

The Schenk, Games, and Chen references contradict rather than support the Examiner's allegations of inadequacy of the PDAPP mouse model. As noted above, Games appeared as the cover story of *Nature* and describes many characteristics of the PDAPP mouse that closely resemble the pathology in Alzheimer's disease. The reference concludes:

A most notable feature of these transgenic mice is their Alzheimer-like neuropathology . . . . Our transgenic model . . . offers a means to test whether compounds that lower A $\beta$  production and/or reduce

its neurotoxicity in vitro can produce beneficial effects in an animal model prior to advancing such drugs into human clinical trials.

*See* p. 527, first column, second paragraph.

Similarly, Schenk, which also formed the cover story of the edition of *Nature* (*see* Schenk *et al.*, *Nature*, 400:173-177 (1999)) in which it appeared, concludes:

To our knowledge, this is the first report of a clinically relevant treatment that reduces the progression of AD-like neuropathology in a transgenic model [the PDAPP mouse] of the disease. . . . Collectively, the results suggest that amyloid- $\beta$  immunization may prove beneficial for both the treatment and prevention of Alzheimer's disease.

*See* p. 177 paragraph bridging cols. 1 and 2.

Finally, Chen (*see* Chen *et al.*, *Progress in Brain Research*, 17:327-337 (1998)) concludes that the PDAPP mouse model, although not displaying all pathological hallmarks of Alzheimer's disease, does "display most of them in a robust manner that increases with age and gene dosage" and provides a "useful model for the testing of various therapeutic interventions directed towards specific aspects of the neurodegenerative process (*see* p. 333, first column, last paragraph). Thus, the cited references support rather than contradict the view that the PDAPP mouse does exhibit many of the pathological characteristics of Alzheimer's disease, and is regarded in the art as a model reasonably predictive of results in humans.

The validity of the PDAPP mouse as a model system for predicting effects of A $\beta$  in humans is further confirmed by human clinical trials. (The Examiner's comments regarding side effects observed in these trials will be addressed separately below.) The Investigational New Drug Application ("INDA") supporting the clinical trials was based on essentially the same data as is contained in the present application. That the FDA allowed clinical trials to occur shows that it considered the preclinical evidence, including the results in PDAPP mouse, as being reasonably predictive of success in humans.

Both symptomatic analysis of patients in a phase I human clinical trial and postmortem analysis of patient in a phase II human clinical trial support the validity of the PDAPP model as a predictor of results in humans and directly provides evidence of a clinical benefit in humans. Data from the phase I human clinical trial showing cognitive effects is described in the attached declaration by Dr. Martin Koller. The declaration describes a phase I trial in which A $\beta$ 42 (42 amino acid form of A $\beta$ , aka AN1792) plus the adjuvant QS-21 was administered to patients suffering with Alzheimer's disease in comparison to a placebo control group (adjuvant alone). The functional disability of patients in this trial was assessed before treatment with A $\beta$  commenced (baseline) and at intervals thereafter. The clinical outcome measure used to measure functional disability was the Disability Assessment for Dementia (DAD) scale. The average DAD score of patients administered placebo declined by 31.38 points from the baseline to final visit. (See Table 1 of the Declaration of Martin Koller.) The decline in score indicates a decline of functional abilities of the patients. The decline of average DAD score of patients administered AN1792/QS-21 was inhibited in each of the three treatment groups. Dr. Koller concludes that the results from the clinical trial provide statistically significant evidence that administration of AN1792(QS-21) to humans is beneficial in treating Alzheimer's disease.

Data from a postmortem analysis of a patient participating in a phase II human clinical trial is described by Nicoll *et al.* (see Nicoll *et al.*, *Nature Medicine*, 9(4):448-452 (April 2003))<sup>1</sup>. After the phase II trial was halted, a woman died from causes unrelated to the trial and her brain was subject to a postmortem analysis. (As previously noted, The Examiner's comments regarding side effects observed in these trials will be addressed separately below.) The analysis showed three major features in common between the brain from the treated human and the brain of a treated PDAPP mouse. First, there were extensive areas with a low-density of A $\beta$  plaques without plaque associated dystrophic neurites and GFAP-immunoreactive astrocytes. Second, A $\beta$  immunoreactivity was associated with microglia in areas devoid of plaques. Third, there was

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<sup>1</sup> Nicoll *et al.* is cited as cite no. 350 on the PTO/SB/08B form attached to the supplemental IDS submitted herewith.

persistence of cerebrovascular amyloid. (See the first column, last paragraph of p. 4.) Thus, the Nicoll paper shows many similarities between treatment of Alzheimer's disease in humans and the PDAPP mouse including "therapeutic modification of the neuropathology of AD with removal of A $\beta$  from the human brain." See p. 4, second column, first paragraph.

Insofar as the rejection is directed to other diseases having similar pathology to Alzheimer's disease (*i.e.*, presence of amyloid deposits of A $\beta$ ), then one would expect similar results. In each case, one would expect that induced antibodies to A $\beta$  would act to prevent further deposition of A $\beta$  and/or clear existing deposits. In each case, one would expect that inhibiting or clearing the underlying pathology would have a similar effect on clinical symptoms of disease that result from the underlying pathology. Insofar as the rejection is directed to other disease characterized by amyloid deposits other than A $\beta$ , the rejection is moot in view of amendments to the claims.

14. The Examiner cites several papers (Lemere, Schenk, DeMattos, and Raso) as evidence that show that therapy can be effective in removal of amyloid plaques. The Examiner does not indicate how any of this evidence detracts from enablement of the present claims. Accordingly, it is believed no response is needed.

15. The Examiner alleges that one would doubt that the claimed method would work due to lack of teaching in the art regarding producing an immune response against an amyloid component (citing Tennent and Stein), lack of information as to specific biological actions that an antigenic composition and an adjuvant would effect, and how the immunogenic effect on amyloid deposition would relate to symptoms of Alzheimer's disease, and expectations that the amyloid peptide would be actively involved in amyloid deposition (citing Kline, U.S. 5,851,996; Potter, U.S. 5,780,587; and, Perutz).

The available evidence contradicts the expectations alleged by the Examiner. The Examples of the application demonstrate that administration of A $\beta$  to a transgenic mouse model generates antibodies to A $\beta$  and clears amyloid deposits. The clearing of amyloid deposits following administration of A $\beta$  indicates that the A $\beta$  is not actively involved in amyloid

deposition, or if it is, that this process is more than counterbalanced by clearance of A $\beta$  by antibodies. It has also been demonstrated in mouse models that clearing of amyloid deposits by antibodies to A $\beta$  improves behavioral characteristics of the mice (*see, e.g.*, Chapman cited on p. 8, paragraph 16 of the office action). The Kline, Potter, and Perutz references provide no reason to think that exogenously supplied A $\beta$ , particularly in combination with an adjuvant, adds to existing plaques rather than clearing plaques as demonstrated in the present examples. Kline discusses treatment with very low dosages of A $\beta$ . Potter discusses screening for compounds that inhibit binding of A $\beta$  to apolipoprotein E4 or alpha-1 antichymotrypsin. These compounds include certain fragments of A $\beta$ . Perutz discusses crystallographic analysis of the structure of amyloid fibers. Thus, none of these references contradicts the evidence in the present application that administration of A $\beta$  with an adjuvant clears A $\beta$  deposits rather than adding to them.

It is not apparent how the cited Stein and Tennent references are relevant to the above issues. Stein discusses expression of several genes in the brains of transgenic mice that may be induced in response to accumulation of A $\beta$ . Tennent discusses a role of serum amyloid P protein in rendering amyloid plaques resistant to degradation. Neither reference appears detrimental to enablement.

16. The Examiner alleges that undue experimentation would be required to evaluate all possible aspects of both humoral and cellular aspects of the immune response. The Examiner cites Chapman, Frenkel (1999), Frenkel (1998), Frenkel (2000), and Friedland (1997) as alleged evidence of the unpredictable effects of antigens on the immune system. In response, an understanding of mechanism is not required to practice the claim as presently formulated. The claims as presently formulated specify that one administers a dosage of an agent effective to induce antibodies to an amyloid component derived from prion precursor protein in combination with an adjuvant that augments the immune response. The result of treating or preventing a prion based disease follows from performing the claims as written without the need to understand how the induced antibodies effect this result.

It is not seen that the cited references are detrimental to enablement. Friedland discusses possible use of labeled A $\beta$  as agent for imaging plaques in the brain. However, the A $\beta$



is not proposed to be administered with an adjuvant or otherwise to generate an immune response comprising antibodies. Thus, there is nothing in Frenkel to suggest that the combination of A $\beta$  and an adjuvant would not be effective in preventing or treating Alzheimer's disease. The various Frenkel references investigate the role of an N-terminal epitope of A $\beta$ , and propose to display it from a phage for use as an immunogen to generate antibodies in a mouse model of Alzheimer's disease. This proposal appears closely related to one embodiment disclosed in the present application (which predates the Frenkel references) (*see* the specification at p. 40, line 23 to p. 50, line 25). That others have incorporated the teaching of the present application into their own work supports rather than refutes enablement of the present claims. Finally, Chapman reviews three papers that test antibodies to A $\beta$  for effects of potential treatments of both brain damage and cognitive losses caused by Alzheimer's disease. Chapman concludes that "All in all, though, these three papers give cause for optimism" (at p. 916, first column, last paragraph). Thus, again Chapman supports rather than contradicts enablement of the present claims.

17. The Examiner alleges undue experimentation would also result from inflammatory side effects (citing to Elan press releases, Grubeck-Loebenstein, and U.S. 5,958,883)<sup>2</sup>. It is respectfully submitted that requiring a patent applicant to teach means for avoiding all side effects imposes too high a standard of enablement. Here, clinical trials have indicated that inflammatory side effects may result in a small number of patients (about 15 out of 360), as discussed in the Elan press releases, and Munch (made of record as cite no. 359). Moreover, in the few patients that might experience side effects, there is the possibility of mitigation by immunosuppressants (*see* Munch at p. 1085). Few approved drugs, particularly those for treating serious diseases, are entirely free of side effects. Moreover, the requirements under the law for obtaining a patent are not as stringent as the requirements for obtaining

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<sup>2</sup> U.S. 5,958,883 discusses an animal model of Alzheimer's disease induced by continuous infusion of A $\beta$  into the brain. This model appears to be similar to that of Tanaka and is therefore addressed by the remarks in paragraph 19.

government approval to market a particular drug for human consumption. *In re Brana*, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). "Testing for full safety and effectiveness...is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." *Id.*

18. The Examiner alleges additional unpredictability with respect to mutants, fragments, and peptides. In response, it is noted that the recitation of mutants, fragments and peptides occurred with respect to the description of a precursor protein in claim 13. Claim 13 has been cancelled.

Insofar as the rejection is directed to fragments, the specification provides several sources of evidence that N-terminal fragments are effective for treatment of Alzheimer's disease. First, the specification describes an example (*see Example IV at p. 75 et seq.*) in which A $\beta$ 1-5 was shown to reduce A $\beta$  deposits in the cortex at statistically significant levels. Second, the specification provides data that three different monoclonal antibodies binding to epitopes 1-5, 3-6 or 3-7 bound to and phagocytosed amyloid deposits (*see Example XI at p. 95 et seq.*). One would expect that N-terminal fragments including epitopes 1-5, 3-6 or 3-7 would generate antibodies having similar specificity to the monoclonals found to induce phagocytosis amyloid deposits, and would therefore achieve similar results. Third, a related application published as WO 00/72880 provides data mapping the epitope specificity of antibodies induced by immunization with A $\beta$ 1-42 (*see Example XVII at p. 101 et seq.*). The data indicate the most of the antibodies bind to epitopes within A $\beta$ 1-11.

Collectively, these experiments show that fragments containing N-terminal epitopes can achieve a clearing response against amyloid deposits. Further, other fragments could be screened using the same methods and same endpoints. The number of fragments of A $\beta$  is not infinite and because many of the various possible fragments of beta amyloid peptide have overlapping sequences, the key regions of peptide needed for pharmacological activity can be determined by screening only a relatively small proportion of the total number of peptides. For example, if it is found that deletion of 20 amino acids from the C-terminus has no lowering of

activity, then one can infer that deletions of fewer amino acids from the C-terminus will also not lower activity. Thus, by testing only a few of the possible fragments of beta amyloid peptide, one can predict whether any other fragment will have pharmacological activity. Therefore, it is submitted that undue experimentation would not be required to identify suitable fragments to use in the methods.

19. The Examiner cites Tanaka as evidence that administration of A $\beta$  to the cerebral ventricle of rats produces learning and memory deficits accompanied by dysfunction in the cholinergic and dopaminergic systems. In response, it is noted that Tanaka administered A $\beta$  without an adjuvant placing his procedure outside the scope of the claims as presently formulated. Further, it is noted that the combination of conditions used by Tanaka was specifically chosen with a view to aggregating A $\beta$  in the brain as a model of Alzheimer's disease rather than clearing such deposits. Thus, Tanaka administered A $\beta$  directed to the brain, by continuous infusion, and without an adjuvant. A skilled person intending to generate an immune response comprising antibodies with a view to clearing A $\beta$  deposits could easily avoid such a combination of conditions calculated to achieve the opposite effect.

20. The Examiner alleges that the application must establish a nexus between the specific immune response recited in the claims for each amyloid disorder and the alleviation of the disease state. The Examiner alleges that the skilled artisan is not guided as to how an immune response must effectuate one or more actuates of each targeted protein such that the immune response would alleviate the disorder. The Examiner also refers to variation between different amyloid disorders (citing Small, Chapman, Esiri, St. George-Hyslop, Younkin, Tennent, and Stein).

As previously discussed, the application does provide evidence that an antibody component of an immune response to peptide administration is, at least in part, responsible for alleviation of the disease state. This is shown by the result that passive immunization with antibodies achieves essentially the same results as active immunization with peptides. Further understanding of mechanisms by which antibodies lead to clearing of amyloid deposits is not

required for practice of the invention. Nevertheless, the application does provide data showing that induction of a phagocytotic clearing response is involved, at least in part. The Examiner's additional comments regarding possible variation between different types of amyloid disease are moot in view of the amendment of the claims to amyloid comprising A $\beta$ .

21-22. The claims are provisionally rejected for same invention double patenting over claims of several copending cases. Applicant requests this issue be held in abeyance until indication of otherwise allowable subject matter. It is likely in view of the restriction and election of species requirements that the claims in the cited cases will differ from those pending in the current case at the time of allowance of the present case. However, if claims from different cases are in conflict at that time, applicant will amend the claims in the cited cases to avoid the conflict.

23-29. The claims stand provisionally rejected for obviousness type double patenting over several copending cases. Applicant proposes the issues be held in abeyance until indication of allowability in the present case. Applicant will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to be patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

30. Claims 11-13, 15 and 16 stand rejected as anticipated by Kline U.S. 5,851,996. Kline is alleged to teach a method of administering A $\beta$  fragments to simulate an immune response to treat or alleviate the symptoms of Alzheimer's disease. This rejection is respectfully traversed.

The claims, particularly as amended, are distinguished over Kline in that Kline does not disclose using an adjuvant that stimulates an immune response. Kline administered his A $\beta$  together with Thimerosal, which is a preservative not an adjuvant. The specification defines an adjuvant as "a compound that when administered in conjunction with an antigen augments the

immune response to the antigen, but when administered alone does not generate an immune response to the antigen. Adjuvants can augment an immune response by several mechanisms including lymphocyte recruitment, stimulation of B and/or T cells, and stimulation of macrophages" (*see* the specification at p. 11, lines 10-14). Although this meaning for adjuvant is commonplace in the field of immunology, applicant notes that the term "adjuvant" is sometimes used more broadly to include compounds that are added to pharmaceutical compositions to increase or aid their effect more generally (*see* the excerpt from American Heritage Dictionary Online, attached hereto as Exhibit C). Applicant has performed a literature search and review to confirm that Thimerosal is regarded as being preservative and not a compound that enhances the immune response (*see* Exhibit D, attached hereto, for further discussion of the literature search strategy and the databases searched.)

In brief, the literature search and review identified numerous references in which Thimerosal is referred to as being a preservative. An excerpt from the article entitled "Thimerosal in Vaccines" from the Center for Biologics Evaluation and Research<sup>3</sup> is typical of the results from the literature search and review.

Thimerosal is a mercury-containing organic compound (an organomercurial). Since the 1930s, it has been widely used as a preservative in a number of biological and drug products, including many vaccines, to help prevent potentially life threatening contamination with harmful microbes.

"Thimerosal in Vaccines" at p. 3.

(*See* Exhibit E, attached hereto, for further discussion of "Thimerosal in Vaccines".)

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<sup>3</sup> The Center for Biologics Evaluation and Research ("CBER") is part of the U.S. Food and Drug Administration, and is responsible for the review and approval of vaccines for human use.

The literature search found two abstracts that refer to Thimerosal as an adjuvant. However, in both of these abstracts and in the full text publications corresponding to the abstracts (all of which are cited in the Supplemental IDS submitted herewith), it was apparent from the context that adjuvant was not being used to denote a component of a composition that enhances an immune response, but more generally simply to refer to a component of a composition having some beneficial function. The Derwent abstract of U.S. Patent No. 5,989,566 erroneously lists Thimerosal as an adjuvant; U.S. Patent No. 5,989,566 actually discloses Thimerosal only as a preservative, not as an adjuvant. (See Exhibit F, attached hereto, for further discussion of the Derwent File 351: Derwent WPI database abstract for U.S. Patent No. 5,989,566 and U.S. Patent No. 5,989,566.) The Chemical Abstracts abstract of the report entitled, "Injection of Newborn Mice with Seven Chemical Adjuvants to Help Determine Their Safety in Use in Biologicals" and the report itself, only refer to Thimerosal as an adjuvant in the title. (See Exhibit G, attached hereto, for further discussion of the Chemical Abstracts database abstract for the report entitled, "Injection of Newborn Mice with Seven Chemical Adjuvants to Help Determine Their Safety in Use in Biologicals"; and, for further discussion of the report itself.)

In short, the literature search and review performed by the applicant provides ample evidence that Thimerosal is a preservative and no evidence at all that it has, or is thought to have, properties that enhance an immune response.

The claims are further distinguished in that Kline also does not expressly or inherently disclose that administration of A $\beta$  under his conditions resulted in an immune response comprising antibodies. Kline does not expressly disclose A $\beta$  acts through generation of antibodies but to the contrary, Kline proposes that his low dosages operate by a negative feedback mechanism whereby administration of A $\beta$  prevents synthesis of further A $\beta$  (see paragraph bridging columns 9 and 10). Further, the dose proposed by Kline does not inherently

generate antibodies to A $\beta$  and thereby treat or prevent Alzheimer's disease. The low dosage of A $\beta$  used by Kline would barely alter the level of endogenous circulating A $\beta$  in humans.<sup>4</sup> Particularly in the absence of an adjuvant, it would seem unlikely that such a regime would result in generation of antibodies. This expectation has been confirmed by an experiment described at pp. 90-94 of the present application. The experiment compared the capacity of A $\beta$ 42 (aka AN1792) to induce antibodies in combination with various adjuvants or Thimerosal or a PBS-only control. The titers from administering 10  $\mu$ g A $\beta$ 42 (the maximum dosage proposed by Kline) in combination with Thimerosal<sup>5</sup> (the preservative recommended by Kline) compared with PBS alone are shown at Table 11, last two rows. The measured titer from administering from 10  $\mu$ g A $\beta$ 42 with Thimerosal alone was not significantly different from the PBS control. By contrast, 100  $\mu$ g A $\beta$ 42 administered in combination with alum, MPL, QS21 or CFA generated titers of the order of 1000's or 10,000's. The above experiment and the size of dosage compared with level of endogenous circulating A $\beta$  strongly suggest that Kline's regime is not suitable for generating antibodies to A $\beta$ . Certainly, one could not reasonably assume that antibodies to A $\beta$  would necessarily result from such a procedure and thereby treat or prevent Alzheimer's disease.

Because Kline does not disclose an adjuvant or a dose that necessarily generates antibodies to A $\beta$ , the reference does not anticipate the pending claims.

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<sup>4</sup> Amounts in the range of  $10^{-10}$  mg to  $10^{-2}$  mg of amyloid protein are discussed by Kline (*see* col. 9, lines 45-49), and a dosage unit of  $10^{-4}$  mg was administered in Examples 1 and 2 (*see* col. 10, lines 32-34 and 46-48). The normal concentration of A $\beta$  in human plasma is typically in the range of 50-200 pg/ml (Seubert *et al.*, *Nature* 359, 325-327 (1992)).

<sup>5</sup> Table 9 does not expressly state that A $\beta$ 42 was administered in combination with the Thimerosal. However, this is clear from the specification at p. 94, lines 12-13.

Application No.: 09/724,953  
Amdt. Submitted on May 27, 2003  
Reply to Office Action of November 27, 2002

PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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